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14. ABSTRACT

Atypical antipsychotics (AAP) are prescribed to millions of patients with neuropsychiatric disorders. Although SGAs can ameliorate mental dysfunctions, they have serious metabolic side-effects such as weight gain, the metabolic syndrome, and increased risk of diabetes and cardiovascular disease. The current dogma is that metabolic side effects of AAP are attributed to their action on neuronal circuits the brain. However, we previously discovered expression of functional dopamine and serotonin receptors in human and rodent adipocytes and proposed that these receptors are targeted by AAP. *In vivo* studies with rats and *in vitro* studies with human adipocytes demonstrated multiple direct effects of AAP on adipose tissue. These include increased food intake, fat accumulation, enlargement of adipocytes, alterations in key metabolic genes, changes in the secretion of leptin and adiponectin and suppression of basal and isoproterenol-stimulated lipolysis. We conclude that AAP-induced metabolic dysregulation is caused, in part, by their direct action on adipose tissue, presumably via the local dopamine and serotonin receptor subtypes.

15. SUBJECT TERMS
Antipsychotics, adipocytes, metabolic syndrome, in vivo, in vitro, dopamine, serotonin, receptors

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Introduction

Atypical antipsychotics (AAP) are used chronically to treat millions of pediatric, adult, and geriatric patients with schizophrenia, bipolar disorder, major depression, post-traumatic stress disorder and autism (1,2). While most drugs alleviate neurobehavioral symptoms, many of the AAPs cause serious metabolic side-effects such as weight gain, metabolic syndrome and increased mortality due to cardiovascular disease (3). The precise targets of AAPs are unclear, but they are known to bind primarily to dopamine and serotonin receptors (4,5). The current dogma is that AAPs bind to these receptors within the brain. However, our laboratory discovered that the same receptors are also expressed in adipose tissue (6) and thus, these drugs can bind to those receptors as well.

Among the most widely prescribed AAP, olanzapine (Zyprexia) and clozapine (Clozaril) carry the greatest risk of the metabolic disturbances, quetiapine (Seroquel) and risperidone (Risperdal) have an intermediate risk, while ziprasidone (Geodon) and aripiprazole (Abilify) confer lower risks (7). **Table 1** shows an example of three AAP and their relative effects on weight gain, glucose homeostasis and dyslipidemia. For our studies, we selected Olanzapine and Zipresidone which represent high and low risk of the metabolic syndrome. The metabolic syndrome is defined as a cluster of disorders that include obesity, insulin resistance, glucose intolerance, hypertension and dyslipidemia, and is associated with increased morbidity, and high risk of mortality due to cardiovascular disease.

Table 1: Metabolic disturbances associated with selected AAP

	Weight Gain	Glucose Abnormalities	Dyslipidemia	Metabolic Syndrome
Olanzapine	High	High	High	High
Risperidone	Medium	Medium-Low	Low	Medium
Ziprasidone	Low	Low	Low	Low

Hypothesis

Direct effects of AAP on selected functions of the adipocytes contribute to weight gain and metabolic dysregulation.

Specific Aims

Aim 1: to determine the *in vivo* effects of oral delivery of AAP on body weight, food intake, and body composition in rats.

Aim 2: to examine changes in gene expression in fat depots from these rats.

Aim 3: to analyze the effects of AAP on lipolysis and adipokine release in mature human adipocytes.

Methods

Rat Model: Adult female Sprague-Dawley rats under normal diet were given cookie dough mixed with Olanzapine or Ziprasidone (4 mg/kg), or vehicle, twice a day for 7 days. Body weight and food intake were measured every day, and body composition by non-invasive NMR was measured on days 1,3, and 7. On days 3 and 7, groups of animals were euthanized and subcutaneous (sc) and periovarian (vis) fat was harvested and analyzed by custom-designed PCR arrays for selected adipose-related genes.

In Vitro Model: Human subcutaneous adipose tissue was obtained with informed consent from patients undergoing elective abdominoplasty procedures. Explants (2-3 mm) were prepared. Mature adipocytes were isolated by collagenase digestion followed by differential centrifugation.

RNA extraction and purification: RNA was isolated using a modified trizol protocol to remove excess triglycerides and produce crude RNA. Purified DNA-free RNA was isolated from crude RNA using a RNAspin mini kit.

RT-qPCR: After reverse transcription, cDNA was analyzed by two methods: 1) custom-designed RNA arrays with 21 metabolic-related genes. β-2 microglobulin (B2M) and hypoxanthine phosphoribosyl

transferase (HPRT) were used as reference genes.

Lipolysis: Adipocytes were incubated with various treatments for 72h and then were incubated with (2h) and without (4h) the β-adrenergic agonist isoproterenol in Krebs-Ringers buffer containing 2% BSA. Glycerol release was measured by colorimetry.

ELISA: Paired commercial capture and detection antibodies were used to analyze leptin or adiponectin by respective sandwich ELISAs using fluorometric detection.

Body

Effects of AAP on body weight, food intake and adiposity in rats

The objective was to compare the effects of treating rats with two AAP: Olanzapine (Olan) and Ziprasidone (Zip) which represent high and low risk of metabolic disturbances. Adult female rats were given cookie dough mixed with vehicle, olanzapine or ziprasidone at 4 mg/kg twice/day for 7 days. **Fig 1** shows rapid increases in food intake and body weight, with olanzapine exhibiting stronger

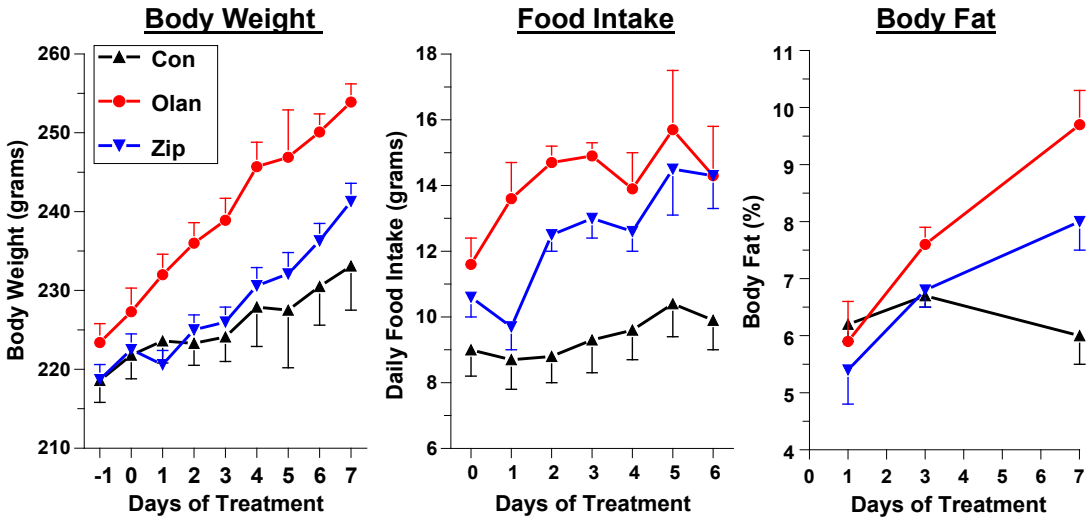

Fig 1: Differential increases in body weight, food intake and body fat induced by olanzapine and ziprasidone. Female rats were given 4 mg/kg of drug or vehicle orally twice/day for 7 days. Each value is a mean±SEM of 8 rats.

effects than ziprasidone. The weight gain was likely due to fat mass expansion, as supported by *in vivo* NMR. Although the olanzapine-induced food intake leveled off after 2-3 days, fat mass continued to rise, suggesting a direct effect of the drug on fat accumulation.

Olanzapine-induced enlargement of adipocytes

Periovarian fat from rats treated with control or olanzapine for 7 days was fixed in paraformaldehyde, embedded in paraffin, sectioned and stained with H&E. **Fig 2** reveals a significant, 60% increase in adipocyte size in response to olanzapine, confirming the data obtained with NMR on fat mass accumulation.

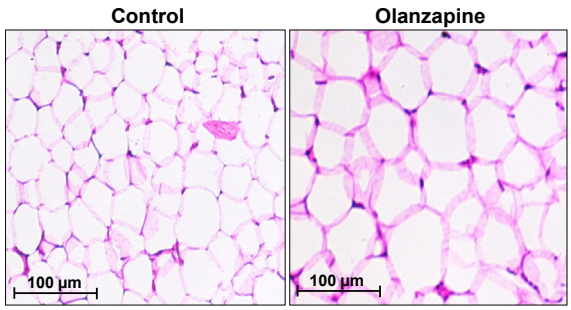

Fig 2: Olanzapine induces enlargement of peri-ovarian adipocytes after 7 days of treatment. Tissue was stained with H&E.

Changes in gene expression

We previously examined the effects of incubating visceral (vis) and subcutaneous (sc) explants from untreated rats with ligands which activate dopamine receptors (DAR), serotonin receptors (5-HTR) and histamine receptors. For that, we selected two key adipokines: leptin and adiponectin, and two key transcription factors: PPARG, which regulates adipogenesis, and SREBP1, which regulates lipid homeostasis (see the 2013 progress report). After establishing the *in vitro* responsiveness of rat adipose tissue to these ligands, our next objective was to determine whether *in vivo* treatment with olanzapine and

ziprasidone alter a larger number of metabolic-related genes. To this end, we used custom-designed PCR array which contain a carefully selected set of genes, grouped by function into: 1) metabolic components, 2) adipokines/cytokines, 3) transcription factors, and 4) various receptors. We examined changes in these genes in both sc and vis fat in response to treatment with the two AAP for 3 and 7 days.

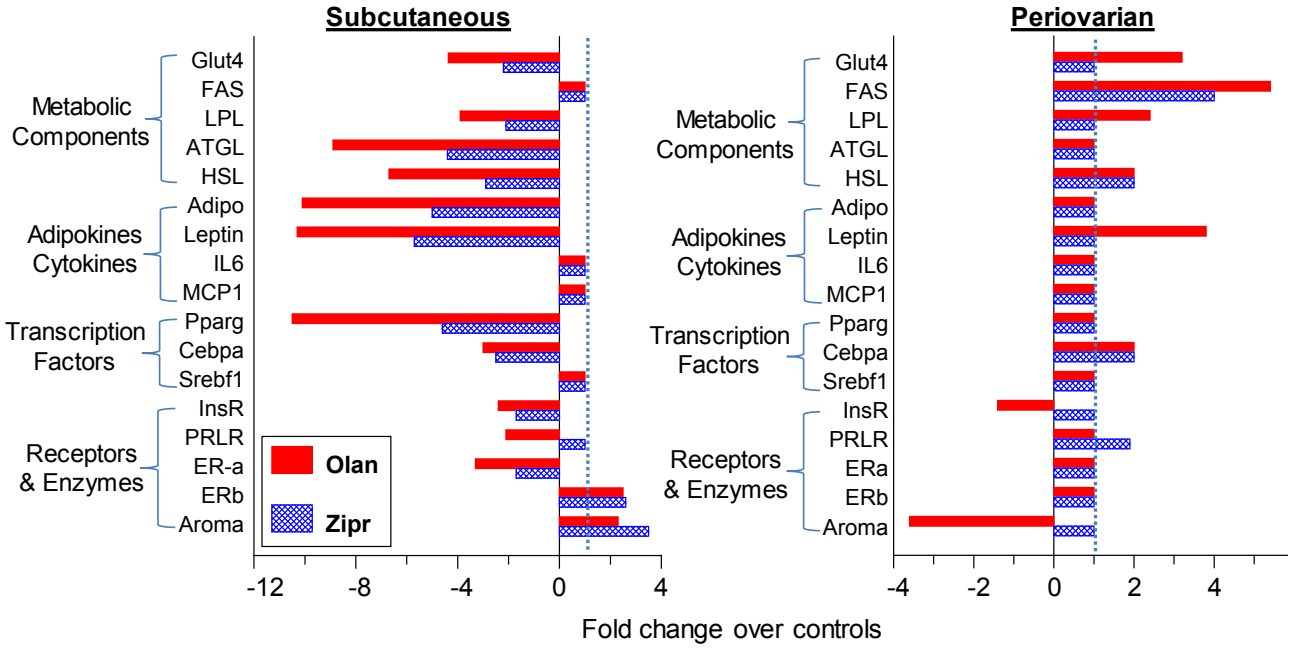

Fig 3: AAP-induced changes in expression of 17 metabolic-related genes in sc and periovarian (vis) adipose tissue. Female rats were orally-treated for 3 days with olanzapine (Olan), ziprasidone (Zipr) or vehicle. Data are expressed as fold positive or negative changes over controls, after correction for 2 house-keeping genes. Blue dotted line = no change.

Fig 3 shows a complex outcome, with many of the genes suppressed in sc, but not in vis, fat after 3 days. Without exception, olanzapine showed stronger effects than ziprasidone. Several key lipolytic enzymes (LPL, ATGL and HSL) as well as transcription factors (PPARγ and c/EBPα) that regulate adipogenesis were suppressed in sc fat, while FAS, the major enzyme that regulates lipogenesis, as well as Glut4, an insulin-regulated glucose transporter, were increased in periovarian fat. Adiponectin and leptin were strongly suppressed in sc fat after 3 days of treatment, while IL-6 and MCP-1 increased after 7 days (data not shown). Insulin receptor expression was moderately suppressed in both fat depots, suggesting induction of insulin resistance. Expression of Srebf1, which regulates lipid homeostasis, significantly increased after 7 days by both drugs (not shown), suggesting a delayed fat accumulation and a potential induction of liver steatosis (8).

Adiponectin, an insulin-sensitizing adipokines, was markedly suppressed in sc fat but did not change in vis fat. Unexpectedly, leptin was markedly suppressed by both drugs in sc fat, but increased in response to olanzapine in vis fat. Since the relative contributions of sc and vis adipose depots to the circulating levels of adipokines/inflammatory is unknown, only their direct analysis is sera following drug treatment should provide a true assessment of their impact on remote targets such as brain, liver or cardiovascular system. Notably, estrogen receptor alpha (ERa) was reduced but estrogen receptor beta (ERb) was moderately increased in sc fat, while aromatase, which converts androgen precursors to estrogens was suppressed. Future research should examine the role of gonadal steroids and their receptors in metabolic homeostasis in response to treatment with AAP.

Alterations in adipokine release from mature sc human adipocytes

Next, we examined the effects of dopamine sulfate (DAS), olanzapine and ziprasidone on leptin and adiponectin release from mature sc human adipocytes. As depicted in **Fig 4**, a 3 day incubation with 1 nM olanzapine caused >65% inhibition of adiponectin release, while 1 nM ziprasidone was without

an effect. Notably, 10 nM olanzapine was less effective than the 1 nM dose, suggesting activation of opposing receptors at higher doses; 10 nM ziprasidone caused 50% inhibition of adiponectin, while DAS was without effects. Ziprasidone, however, was more effective than olanzapine in suppressing

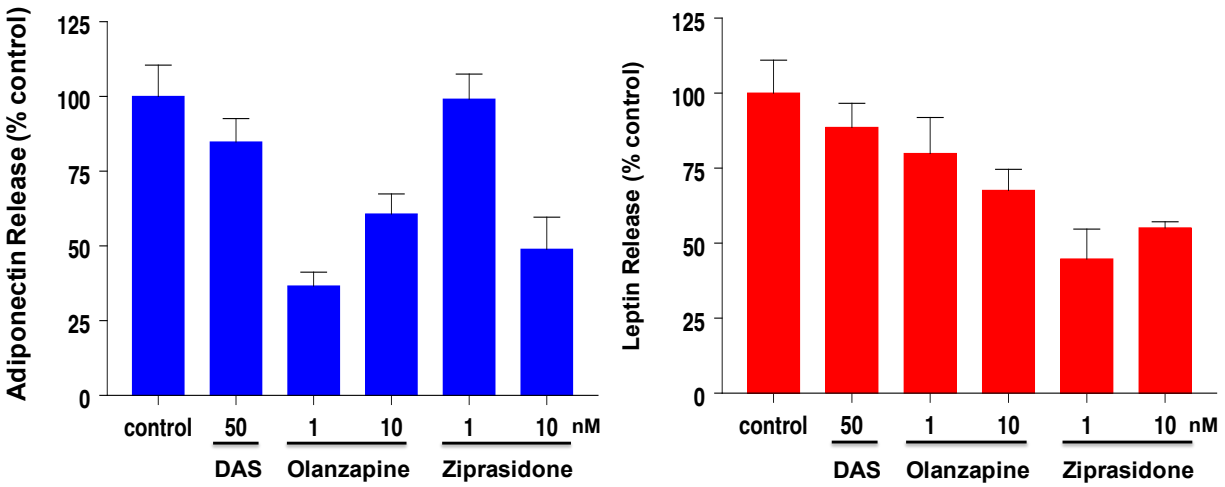

Fig 4: Effects of dopamine sulfate (DAS), Olanzapine, or Ziprasidone on adiponectin (*left panel*) and leptin (*right panel*) release from sc mature human adipocytes incubated for 72 hrs. Media were analyzed by sandwich ELISA.

leptin release, without an obvious dose-dependent actions. This experiments suggests that future studies should identify which receptors mediate the actions of olanzapine vs ziprasidone.

Inhibition of basal and isoproterenol-stimulated lipolysis

The next experiment examined whether incubation of mature sc human adipocytes with DAS, olanzapine and ziprasidone affected lipolysis, as determined by glycerol release. **Fig 5** shows a moderate 15-20% suppression of basal lipolysis by DAS, as well as by 10 nM of either olanzapine or ziprasidone. A similar inhibition of isoproterenol-stimulated lipolysis was seen by DAS and olanzapine, but ziprasidone was either ineffective or slightly stimulatory. This complex outcome suggest again mediation of the two AAP by different receptors.

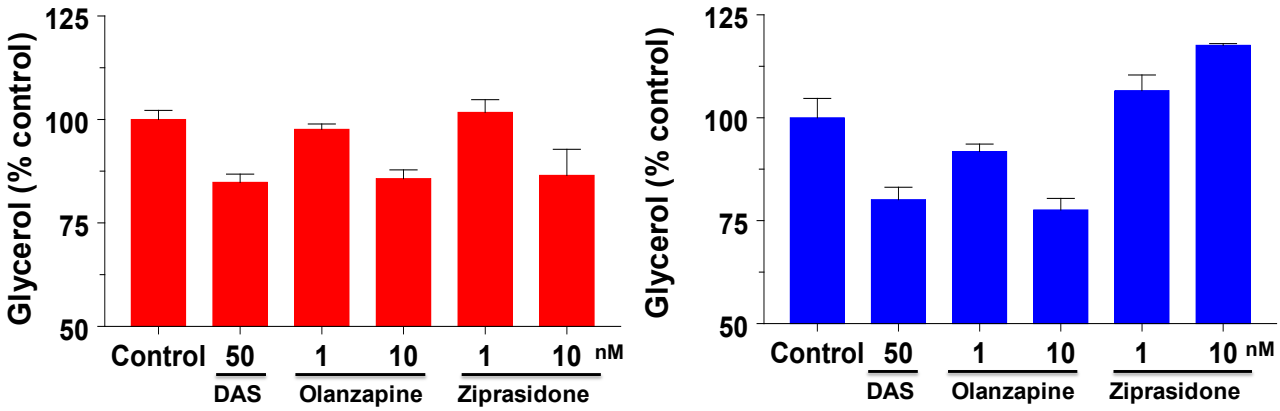

Fig 5: Effects of dopamine sulfate (DAS), Olanzapine, or Ziprasidone on basal (*left panel*) and isoproterenol-stimulated (*right panel*) lipolysis.

Key Research Accomplishments

- ❖ AAP administration in rats results in rapid increases in body weight, food intake and adiposity.
- ❖ Multiple metabolic-related genes are altered in both sc and vis fat in response to *in vivo* administration of AAP.
- ❖ Olanzapine, known to cause more severe metabolic disturbances in humans, was also more

potent in causing metabolic alterations in rats.

- ❖ Studies with isolated human adipocytes demonstrate direct effects of the AAP on both adipokine release and lipolysis.

Reportable Outcome

Presentations in Scientific Meetings:

- ❖ Ben-Jonathan: Antipsychotics induced obesity: **Direct actions on the Adipocytes**, Invited Speaker, the 2014 Obesity Summit, April 2014, London, UK (Appendix 1)
  .
- ❖ Eric R Hugo, Randall R Sakai, Eric J Phillips, Sejal R Fox, Vidjaya LV Premkumar, Nira Ben-Jonathan: **Direct Effects of Weight-Inducing Antipsychotics on Adipose Tissue from Humans and Rats,** Annual Meeting of the Endocrine Society, Chicago, Illinois, June 2014 (Appendix 2).

Conclusion

We are progressing well towards our goal of establishing the direct effects of atypical antipsychotics on adipose tissue functions. Our data lend a strong support to our hypothesis that AAP-induced alterations in patients are due, in part, to their direct actions on the adipocytes. We are currently preparing a manuscript which describes our findings, to be submitted to an high impact, peer reviewed, journal.

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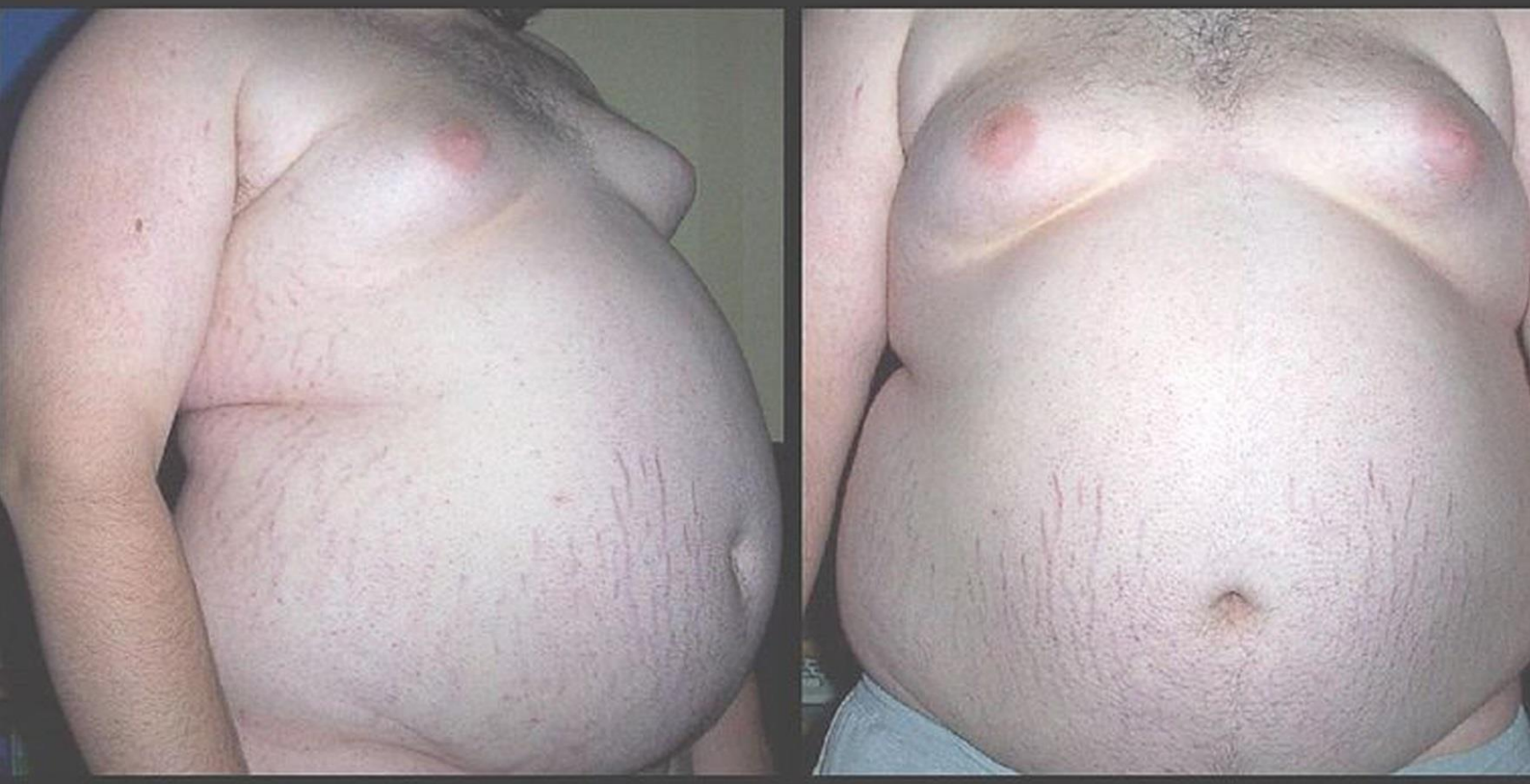
ABSTRACTS



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Day 3: Anti-Obesity Drug Discovery and Development

Invited Speakers Abstracts

Pharmacotherapy for obesity: limited options but plenty of ideas

Professor Jon Arch, Dean of Science, Medicine & Dentistry, University of Buckingham
Professorial Research Fellow and Deputy Director of Metabolic Research, Clore Laboratory,Buckingham Institute of Translational Medicine,University of Buckingham, UK

Almost the only drug available for the treatment of obesity outside the US and Japan is the pancreatic lipase inhibitor orlistat, which is little-used. In the US the old amphetamine-like drug phentermine is by far the most prescribed drug. Phentermine combined with topiramate, and lorcaserin have been approved but sales have been poor and they have not been approved by the EMA. NDAs have been filed for liraglutide. Niche obesity markets may allay safety fears. Brown adipose tissue appears to offer many drug targets, but drugs will have to improve upon past or cheaper approaches to its activation.

Molecular Characterization of White and Brown Adipocytes Reveals Complex Phenotypes

Andrea Worschech[1], Melissa Kazantis[2], Martin Wabitsch[3], Mouaadh Abdelkarim[1], Vladimir Zilberfarb[4], Muriel Strosberg[5], A. Donny Strosberg[6] and Lotfi Chouchane[1]

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[3] Department of Paediatrics and Adolescent Medicine, Division of Pediatric Endocrinology and Diabetology, Ulm, Germany
[4] Institut Cochin INSERM U1016, Université Paris 7-Denis-Diderot, Paris, France
[5] Hepcco, Palm Beach Gardens, Florida, USA
[6] Department of Infectology, The Scripps Research Institute-Florida, Jupiter, FL, USA

Introduction: Over the last two decades the prevalence of obesity has reached epidemic levels not only in highly industrial countries but also worldwide. Secondary major health risks, such as hypertension, insulin resistance, type 2 diabetes and cardiovascular diseases, can be summarized as the metabolic syndrome and are highly associated with obesity. In cases in which energy intake e.g. through high caloric food intake exceeds energy expenditure the overall energy homeostasis is imbalanced. This excess energy is stored in the body in form of white fat, which eventually results in obesity. White adipose tissue (WAT) depots therefore, mainly act as the body's main energy storage and additionally act as an endocrine organ by releasing adipokines and cytokines into the body. Additionally, functional brown adipose tissue (BAT) has recently been discovered through radiological detection by several research groups in the last years in substantial amount in adults. Formerly overlooked BAT, which was thought to be absent in the human adult, has therefore recently become an interesting anti-obesity target due to its ability to dissipate energy in form of heat.

Methods: We cultured and extensively characterized human brown PAZ6 adipocytes in comparison with a white adipose cell line SW872. In addition, human SGBS adipocytes were included in the analysis. Brown and white adipocyte markers were tested by quantitative Real-time PCR. Fluorescent and Oil-Red staining assessed the quantity and quality of the differentiation process. Next generation RNA sequencing of undifferentiated and mature SGBS and PAZ6 cells was performed in order to elucidate pathways distinctly activated in white vs. brown human adipocytes. Functional assessment of oxidative rates of each cell line was conducted using the Seahorse technology.

Results: Whereas PAZ6 and SW872 cells showed classical molecular and phenotypic markers of brown and white adipocytes, respectively, SGBS cells presented a versatile phenotype of adipocyte. 14 days after initiating the differentiation process the expression of classical brown marker such as UCP-1 and PPARg peaked and declined until day 28. The white adipocyte marker Tcf21 however, showed reciprocal behavior. Interestingly, Leptin levels peaked at day 28 whereas the highest adiponectin mRNA levels were monitored at day 14. Phenotypic analysis of the abundance and shape of lipid droplets were consistent with the molecular patterns. On day 14, SGBS cells showed multiple small droplets, however the number of droplets decreased and the size increased until day 28 as expected for a white adipocyte phenotype. Lastly, functional metabolic analysis showed the highest oxidative rate of mature SGBS cells on Day 14, which remained consistent or slightly decreased until day 28.

Conclusion: SGBS cells are widely used as a model for white adipocytes. Our data suggest that the cell line harbors a versatile phenotype, which changes throughout their mature stage. Day 14 displays multiple characteristics of brown fat cells such as UCP-°©-1 overexpression whereas day 28 is representing a rather white phenotype. Many reports suggest recently that the traditional classification of adipocytes is not exclusive and the existence of beige/brite adipocytes has been shown. We are presenting data derived from a human cell line model, which harbors characteristics of both distinct phenotypes. This unique situation allows the study of molecular switches and pathways involved in the conversion between white and brown adipocytes. This knowledge will be of importance for studies aimed to increase brown fat depots in order to increase energy expenditure in obese subjects with the ultimate goal of weight reduction.

Acknowledgment: This work was supported by Weill Cornell Medical College in Qatar, and by a grant from Qatar National Research Fund (NPRP 4-294-3-092). The contents are solely the responsibility of the authors and do not necessarily represent the official views of the Qatar National Research Fund.

Galanin-like peptide (GALP) have anti-obesity effect via the activation of hepatic lipid metabolism

Dr Satoshi Hirako, Post-doctoral fellow, Dept of Anatomy, Showa University School of Medicine, Tokyo, Japan

Galanin-like peptide (GALP) is produced in neurons in the hypothalamic arcuate nucleus and is well known as a neuropeptide regulating feeding behavior and energy metabolism. In this study anti-obesity effect was obtained by the 7-day intranasal administration of GALP in obese mice. The respiratory exchange ratio (RER) of GALP group was lower than the saline group. In addition, fatty acid oxidation-related gene mRNA levels were increased in liver by administration of GALP. The present study indicates that anti-obese effect of GALP may be caused by anorexigenic effect and improvement of lipid metabolism in the liver.

Thiol redox state as a novel pharmacologic target for obesity

Dr Amany Elshorbagy, Visting Postdoctoral Research Fellow, Lecturer in Medical Physiology, University of Oxford, UK Universityi of Alexandria, Egypt

Mouse knockouts of several enzymes in the sulfur amino acid pathway are characterized by increased energy expenditure and resistance to diet-induced obesity. Common to these models is decreased cysteine synthesis and/or plasma total cysteine, and profound hepatic suppression of the key lipogenic enzyme stearoyl-coenzyme A desaturase-1. This talk will include our latest data on using thiol-modifying drugs in mice to control fat mass. Pilot studies using 2 such drugs have shown promising results. The concept is novel, and builds on epidemiologic work showing that plasma total concentration of the thiol amino acid cysteine is one of the strongest parameters associated with fat mass in humans.

Antipsychotics induced obesity: Direct actions on the adipocytes

Professor Nira Ben-Jonathan, Professor of Cancer and Cell Biology, University of Cincinnati, United States

Atypical antipsychotics (AAP) are prescribed to millions of patients with mental diseases. Although AAP ameliorate mental dysfunctions, they have serious metabolic side-effects such as weight gain, diabetes, and cardiovascular disease. We discovered expression of functional dopamine and serotonin receptors in human adipocytes and found that AAP altered many of their functions. We propose that direct actions of AAP on adipose tissue contribute to weight gain and the metabolic syndrome. Human

adipocytes could be integrated into the screening paradigm of candidate new drugs for the identification of undesirable metabolic activities prior to costly animal studies and clinical trials.

Hypothalamic proopiomelanocortin (POMC) down regulation after weaning is associated with hyperphagia-induced obesity in JCR rats over-expressing neuropeptide Y

Dr Abdoulaye Diané,University of Alberta, Edmonton, Alberta, Canada

Poster Presentations

CLINICO-ECONOMIC ANALISIS OF METABOLIC SYNDROME'S TREATMENT.

I.M. Sechenov´s First Moscow State Medical University, Russia.
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Russia, Moscow sb., Ramenskoe, K. Marks str., 8-3, 140100; vera2k@mail.ru

Objective: to compare efficacy of the two schemes of treatment of metabolic syndrome (MS): lifestyle modification and the complex therapy (lifestyle modification + orlistat + metformin) based on results of pharmacoeconomic analysis.

Methods: A total of 60 patients with MS was included in the study. The study group (30 subjects mean age 41,0±11 years, women - 23 (76.7%)) received the complex therapy of MS – lifestyle modification, orlistat 120 mg x 3 t./day and metformin 850 mg x 2 t./day. Control group (30 patients mean age 43,4±9.5 years, women - 26 (86,7%)) was treated with lifestyle modification. At the stage of inclusion in the study and after 6 months of therapy all patients underwent clinical and laboratory investigation and assessment quality of life (QL) according to the SF-36 questionnaire. We constructed a multi-state life-table based Markov model in Excel in which presents of MS influences the incidence of stroke, myocardial infarction (MI), type 2 diabetes mellitus (DM-2) and death. Risk reduction in the control group based on the data of clinical trials that modest weight loss would be lower risk of type 2 DM, but not affect risks of MI and stroke. Risk reduction in study group based on data of clinical trials that weight loss ≥10% and blood pressure ≥12/8 mm hg will reduce both the risk of DM-2, MI and stroke. We use data on risks of MI, stroke and DM-2 identified from PubMed searches, on disease costs from the Russian pharmacoeconomic researches, and on drug costs from the average cost for Moscow and Department of Health. We use a lifetime horizon for costs and health outcomes. Health effects measured as QALYs and costs in Euro, discounted 5%. To assess the dependence of the results of input parameters we conducted sensitivity analysis. To assess the value of 1 QALY used willingness to pay ratio (wtR), equal to three times the size of GDP. Based on wtR, QALY and direct costs was calculated NMB (net monetary benefit) for each therapy.

Results: We received more significant improvement of all clinical outcomes (body weight and blood pressure, glucose and fat metabolism indices) and QL in study group compared with the control. The simulation results showed that the complex therapy of MS allows increasing the average life expectancy for 2,3 years and prevents 4 death, 3 cases of MI, 1 stroke and 8 new cases of DM-2 in a group of 100 patients for 20 years. The standard treatment of MS allows increasing the average life expectancy for 0,7 years and prevents 1 death, 2 cases of MI, 0 stroke and 4 new cases of DM-2 in a group of 100 patients for 20 years. NNT for complex therapy is 6.3, for standard treatment – 16,7. QALY for complex therapy is 9,45, for standard treatment – 8,63. The cost-utility analysis showed that cost per 1 QALY is 1284 € (1220 € discounted) for standard therapy and 1077 € (1023 € discounted) for complex treatment of MS. wtR for Russian Federation is 29 071 €. NMB is 239 798 € (240 352 € discounted) for standard therapy and 264 544 € (265 053 € discounted) for complex therapy of MS. depending of input parameters. Sensitivity analysis showed that regardless of the input parameters, complex therapy of MS will be a priority.

Conclusions: it is shown that the complex therapy of MS, including pharmacotherapy of obesity and insulin resistance is a priority compared with standard therapy, as characterized by the best results of NNT, LYG, QALY, CUR and NMB.

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Direct Effects of Weight-Inducing Antipsychotics on Adipose Tissue from Humans and Rats

Eric R Hugo, PHD, MS[1], Randall R Sakai, PhD[2], Eric J Phillips, B.Sc[1], Sejal R Fox, B.Sc[1], Vidjaya LV Premkumar, Ph.D.[1] and Nira Ben-Jonathan, MS, PHD[1], (1)Cancer Biology, University of Cincinnati, Cincinnati, OH, (2)Psychiatry, Univ of Cincinnati, Cincinnati, OH

Abstract Text:

Background: Second generation antipsychotics (SGA) are prescribed to millions of patients with neuropsychiatric disorders. Although SGAs can ameliorate mental dysfunctions, they have serious metabolic side-effects such as weight gain, the metabolic syndrome, and increased risk of diabetes and cardiovascular disease. The primary therapeutic targets of SGAs are dopamine (DAR) and serotonin (5-HTR) receptors. The current dogma is that metabolic side effects of SGAs are attributed to their action on the brain. We recently discovered expression of functional DAR and 5-HTR subtypes in human and rodent adipocytes and speculated that these receptors are targeted by SGA.

Hypothesis: Direct effects of SGA on selected adipocyte functions contribute to weight gain and metabolic dysregulation.

Methods: *in vitro* model: Subcutaneous (sc) adipose explants and mature adipocytes were harvested from patients undergoing abdominoplasty. Both sc and periovarian (visceral) explants were obtained from female Sprague-Dawley rats. Samples were incubated with 1-100 nM olanzapine or ziprasidone for 72 h and analyzed for lipolysis by glycerol release and for a panel of metabolic-related genes by qRT-PCR. *In vivo* model: Rats were treated with olanzapine or ziprasidone in cookie dough for 3 or 7 days. Food intake, body weight, and fat accumulation (by NMR) were determined. Periovarian and sc adipose explants were analyzed by qRT-PCR for the gene panel as above. Serum leptin and adiponectin were determined by ELISA.

Results: Olanzapine, and to a lesser extent ziprasidone, caused marked suppression of leptin and adiponectin, and modest suppression of basal and isoproterenol-stimulated lipolysis from human sc adipose explants and mature adipocytes, respectively. Treatment of rats with SGA rapidly increased food intake and body weight and a delayed increase in fat accumulation. In sc fat, SGA caused over 5-fold suppression of key lipases, leptin, adiponectin, and PPARg, but a significant stimulation of SREBP.

Conclusion: SGA-induced metabolic dysregulation is caused, in part, by their direct action on adipose tissue, presumably via the local DAR and/or 5-HTR subtypes. We suggest that adipocytes should be integrated into the screening paradigm of candidate new antipsychotics to identify undesirable metabolic characteristics prior to costly animal studies and clinical trials. The long term goal is to provide safer drugs to patients requiring treatment with these medications.

Title: Direct Effects of Weight-Inducing Antipsychotics on Adipose Tissue from Humans and Rats

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